Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
21st Prioritisation – 4th quarter 2014

General Information, efficacy and safety data

Anna Nachtnebel

Introduction

As part of the project „Horizon Scanning in Oncology“ (further information can be found here: http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie), 9 information sources are scanned frequently to identify emerging anticancer drugs.

Every 3 months, these anticancer therapies are filtered (i.e. in most cases defined as availability of phase III results; for orphan drugs also phase II) to identify drugs at/around the same time as the accompanying drug licensing decisions of the EMA.

An expert panel consisting of oncologists and pharmacists then applies 5 prioritisation criteria to elicit those anti-cancer therapies which might be associated with either a considerable impact on financial resources or a substantial health benefit.

For the 21st prioritisation (December 2014), 12 were filtered out of 169 identified drugs and were sent to prioritisation. Of these, 6 drugs were ranked as ‘highly relevant’ by the expert panel, 5 as ‘relevant’ and 1 as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

The summary judgements of the expert panel for all drugs are provided in the following table.

No	Filtered Drugs - 20th prioritisation 3rd quarter 2014	Overall category
1.	Vandetanib (Zactima®) for 2nd line therapy of advanced or metastatic NSCLC	Relevant
2.	Bevacizumab (Avastin®) plus chemotherapy as 2nd line therapy for HER2 negative locally recurrent or metastatic breast cancer that has progressed after first-line treatment with bevacizumab plus chemotherapy	Highly relevant
3.	Bevacizumab (Avastin®) maintenance therapy in HER2-negative metastatic breast cancer that has not progressed during first-line docetaxel plus bevacizumab therapy	Highly relevant
4.	Adjuvant trastuzumab (Herceptin®) in node-positive, HER2 positive breast cancer patients	Highly relevant
5.	Olaparib (Lynparza®) for the maintenance treatment of platinum‑sensitive relapsed BRCA‑mutated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer	Relevant
6.	Gemcitabine (Gemzar®) prior to autologous stem cell transplant for relapsed or refractory aggressive histology non-hodgkin's lymphoma	Relevant
7.	Panobinostat (Faridak®) for relapsed multiple myeloma	Relevant
8.	Cobimetinib (GDC-0973, XL-518) for the first-line therapy of unresectable locally advanced or metastatic melanoma	Highly relevant
9.	Nivolumab (BMS-936558, MDX1106, ONO4538) as first line therapy for unresectable or metastatic melanoma	Highly relevant
10.	Irinotecan (Campto®) in advanced gastric adenocarcinoma	Not relevant
11.	Oxaliplatin (Eloxatin®) for the adjuvant therapy of stage II, IIIa and IIIb gastric adenocarcinoma	Relevant
12.	Bevacizumab (Avastin®) for stage IVB, recurrent or persistent carcinoma of the cervix	Highly relevant

1 Breast Cancer

1.1 Bevacizumab (Avastin®) plus chemotherapy as 2nd line therapy for HER2 negative locally recurrent or metastatic breast cancer that has progressed after first-line treatment with bevacizumab plus chemotherapy

Drug description: anti-VEGF antibody

Incidence in Austria: 5,400 breast cancer patients

EMA/FDA licensing for this indication: -/-

Phase III results:

Minckwitz et al. *Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial.* The Lancet Oncology (2014) 15 (11) 1269 – 1278.

Background

Combining bevacizumab with first-line or second-line chemotherapy improves progression-free survival in HER2-negative locally recurrent or metastatic breast cancer. We assessed the efficacy and safety of further bevacizumab therapy in patients with locally recurrent or metastatic breast cancer whose disease had progressed after treatment with bevacizumab plus chemotherapy.

Methods

Using In this open-label, randomised, phase 3 trial, we recruited patients who had HER2-negative locally recurrent or metastatic breast cancer that had progressed after receiving 12 weeks or more of first-line bevacizumab plus chemotherapy from 118 centres in 12 countries. Patients were randomly assigned (1:1) by use of a central interactive voice response system using a block randomisation schedule (block size four) stratified by hormone receptor status, first-line progression-free survival, selected chemotherapy, and lactate dehydrogenase concentration, to receive second-line single-agent chemotherapy either alone or with bevacizumab (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks). Second-line therapy was continued until disease progression, unacceptable toxicity, or consent withdrawal. At progression, patients randomly assigned to chemotherapy alone received third-line chemotherapy without bevacizumab; those randomly assigned to bevacizumab continued bevacizumab with third-line chemotherapy. The primary endpoint was progression-free survival from randomisation to second-line progression or death in the intention-to-treat population. This trial is ongoing, and registered with ClinicalTrials.gov, number NCT01250379.

Results

Between Feb 17, 2011, and April 3, 2013, 494 patients were randomly assigned to treatment (247 in each group). The median duration of follow-up at the time of this prespecified primary progression-free survival analysis was 15·9 months (IQR 9·1–21·7) in the chemotherapy-alone group and 16·1 months (10·6–22·7) in the combination group. Progression-free survival was significantly longer for those patients treated with bevacizumab plus chemotherapy than for those with chemotherapy alone (median: 6·3 months [95% CI 5·4–7·2] vs 4·2 months [3·9–4·7], respectively, stratified hazard ratio [HR] 0·75 [95% CI 0·61–0·93], two-sided stratified log-rank p=0·0068). The most common grade 3 or more adverse events were hypertension (33 [13%] of 245 patients receiving bevacizumab plus chemotherapy vs 17 [7%] of 238 patients receiving chemotherapy alone), neutropenia (29 [12%] vs 20 [8%]), and hand-foot syndrome (27 [11%] vs 25 [11%]). Grade 3 proteinuria occurred in 17 (7%) of 245 patients receiving combination therapy and one (<1%) of 238 patients receiving chemotherapy alone. Serious adverse events were reported in 61 (25%) of 245 patients receiving bevacizumab plus chemotherapy versus 44 (18%) of 238 patients receiving chemotherapy alone.

Conclusion
These results suggest that continued VEGF inhibition with further bevacizumab is a valid treatment option for patients with locally recurrent or metastatic HER2-negative breast cancer whose disease was stabilised or responded to fi rst-line bevacizumab with chemotherapy.

1.2 Bevacizumab (Avastin®) maintenance therapy in HER2-negative metastatic breast cancer that has not progressed during first-line docetaxel plus bevacizumab therapy

Drug description: anti-VEGF antibody
Incidence in Austria: 5,400 breast cancer patients
EMA/FDA licensing for this indication: -/-
Phase III results:

Gligorov et al. ***Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial*** **The Lancet Oncology (2014) 15 (12) 1351-1360.**

Background
Longer duration of first-line chemotherapy for patients with metastatic breast cancer is associated with prolonged OS and improved progression-free survival. We investigated capecitabine added to maintenance bevacizumab after initial treatment with bevacizumab and docetaxel in this setting.

Methods
We did this open-label randomised phase 3 trial at 54 hospitals in Brazil, China, Egypt, France, Hong Kong, India, Italy, Poland, Spain, and Turkey. We enrolled patients with HER2-negative measurable metastatic breast cancer; each received three to six cycles of first-line bevacizumab (15 mg/kg) and docetaxel (75–100 mg/m²) every 3 weeks. Progression-free patients were randomly assigned with an interactive voice-response system by block (size four) randomisation (1:1) to receive either bevacizumab and capecitabine or bevacizumab only (bevacizumab 15 mg/kg on day 1; capecitabine 1000 mg/m² twice per day on days 1–14, every 3 weeks) until progression, stratified by oestrogen receptor status (positive vs negative), visceral metastases (present vs absent), response status (stable disease vs response vs non-measurable), and lactate dehydrogenase concentration (≤1·5 vs >1·5 × upper limit of normal). Neither patients nor investigators were masked to allocation. The primary endpoint was progression-free survival (from randomisation) in the intention-to-treat population.

Results
Between July 16, 2009, and March 7, 2011 (when enrolment was prematurely terminated), 284 patients received initial bevacizumab and docetaxel; 185 (65%) were randomly assigned (91 to bevacizumab and capecitabine versus 94 to bevacizumab only). Progression-free survival was significantly longer in the bevacizumab and capecitabine group than in the bevacizumab only group (median 11·9 months [95% CI 9·8–15·4] vs 4·3 months [3·9–6·8]; stratified hazard ratio 0·38 [95% CI 0·27–0·55]; two-sided log-rank p<0·0001), as was overall survival (median 39·0 months [95% CI 32·3–not reached] vs 23·7 months [18·5–31·7]; stratified HR 0·43 [95% CI 0·26–0·69]; two-sided log-rank p=0·0003). Results for time to progression were consistent with those for progression-free survival. 78 (86%) patients in the bevacizumab and capecitabine group and 72 (77%) in the bevacizumab only group had an objective response. Clinical benefit was recorded in 92 (98%) patients in the bevacizumab alone group and 90 (99%) in the bevacizumab and capecitabine group. Mean change from baseline in global health score did not differ significantly between groups. Grade 3 or worse adverse events during the maintenance phase were more common with bevacizumab and capecitabine than with bevacizumab only (45 [49%] of 91 patients vs 25 [27%] of 92 patients). The most common grade 3 or worse events were hand–foot syndrome (28 [31%] in the bevacizumab and capecitabine group vs none in the bevacizumab alone group), hypertension (eight [9%] vs three [3%]), and proteinuria (three [3%] vs four [4%]). Serious adverse events were reported by ten (11%) patients in the bevacizumab and capecitabine group and seven (8%) patients in the bevacizumab only group.

Conclusion

Despite prematurely terminated accrual and the lack of information about post-progression treatment, both progression-free survival and overall survival were significantly improved with bevacizumab and capecitabine compared with bevacizumab alone as maintenance treatment. These results might inform future maintenance trials and current first-line treatment strategies for HER2-negative metastatic breast cancer.

1.3 Adjuvant trastuzumab (Herceptin®) in node-positive, HER2 positive breast cancer patients

Drug description: a humanized antibody designed to target and block the function of HER2 protein overexpressing cells

Incidence in Austria: 5,400 breast cancer patients

EMA/FDA licensing for this indication: -/-

Phase III results:

- **Perez et al. *Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Joint Analysis of Data From NCCTG N9831 and NSABP B-31;* JCO (2011) 29 (25); 3366-3373.**

Background
Trastuzumab is a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). The clinical benefits of adjuvant trastuzumab have been demonstrated in interim analyses of four large trials. Initial data of the combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial were reported in 2005. Long-term follow-up results on disease-free survival (DFS) and overall survival (OS) have been awaited.

Methods
Patients with HER2-positive operable breast cancer were randomly assigned to doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab in the NCCTG N9831 and NSABP B-31 trials. The similar design of both trials allowed data from the control and trastuzumab containing arms to be combined in a joint analysis.

Results
At 3.9 years of median follow-up, there continues to be a highly statistically significant reduction in DFS event rate in favor of the trastuzumab-containing arm (P<.001). Similarly, there continues to be a statistically significant 39% reduction in death rate in favor of the trastuzumab-containing arm (P<.001).

Conclusion
These data demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over time, with the longest follow-up reported to date. The clinical benefits continue to outweigh the risks of adverse effects.

- **Perez et al. *Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831* JCO (2014) 32 (33); 3744-3752.**

Background
Positive interim analysis findings from four large adjuvant trials evaluating trastuzumab in patients with early-stage human epidermal growth factor receptor 2 (HER2) –positive breast cancer were first reported in 2005. One of these reports, the joint analysis of North Central Cancer Treatment Group NCCTG N9831 (Combination Chemotherapy With or Without Trastuzumab in Treating Women With HER2-Overexpressing Breast Cancer) and the National Surgical Adjuvant Breast and Bowel Project NSABP B-31 (Doxorubicin and Cyclophosphamide Plus Paclitaxel With or Without Trastuzumab in

Treating Women With Node-Positive Breast Cancer That Overexpresses HER2), was updated in 2011. We now report the planned definitive overall survival (OS) results from this joint analysis along with updates on the disease-free survival (DFS) end point.

Methods
In all, 4,046 patients with HER2-positive operable breast cancer were enrolled to receive doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in both trials. The required number of events for the definitive statistical analysis for OS (710 events) was reached in September 2012. Updated analyses of overall DFS and related subgroups were also performed.

Results
Median time on study was 8.4 years. Adding trastuzumab to chemotherapy led to a 37% relative improvement in OS (hazard ratio [HR], 0.63; 95% CI, 0.54 to 0.73; P<.001) and an increase in 10-year OS rate from 75.2% to 84%. These results were accompanied by an improvement in DFS of 40% (HR, 0.60; 95% CI, 0.53 to 0.68; P<.001) and increase in 10-year DFS rate from 62.2% to 73.7%. All patient subgroups benefited from addition of this targeted anti-HER2 agent.

Conclusion
The addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early-stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence.

2 Melanoma

2.1 Cobimetinib (GDC-0973, XL-518) for the first-line therapy of unresectable locally advanced or metastatic melanoma

Drug description: a MEK inhibitor

Incidence in Austria: advanced melanoma with BRAF mutations: 25-33

EMA/FDA licensing for this indication: -/-

Phase III results:

Larkin et al. *Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma* NEJM (2014) 371: 1867-1876.

Background
The combined inhibition of BRAF and MEK is hypothesized to improve clinical outcomes in patients with melanoma by preventing or delaying the onset of resistance observed with BRAF inhibitors alone. This randomized phase 3 study evaluated the combination of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib.

Methods
We randomly assigned 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation–positive melanoma to receive vemurafenib and cobimetinib (combination group) or vemurafenib and placebo (control group). The primary end point was investigator-assessed progression-free survival.

Findings
The median progression-free survival was 9.9 months in the combination group and 6.2 months in the control group (hazard ratio for death or disease progression, 0.51; 95% confidence interval [CI], 0.39 to 0.68; P<0.001). The rate of complete or partial response in the combination group was 68%, as compared with 45% in the control group (P<0.001), including rates of complete response of 10% in the combination group and 4% in the control group. Progression-free survival as assessed by independent review was similar to investigator-assessed progression-free survival. Interim analyses of overall survival showed 9-month survival rates of 81% (95% CI, 75 to 87) in the combination group and 73% (95% CI, 65 to 80) in the control group. Vemurafenib and cobimetinib was associated with a nonsignificantly higher incidence of adverse events of grade 3 or higher, as compared with vemurafenib and placebo (65% vs. 59%), and there was no significant difference in the rate of study-drug discontinuation. The number of secondary cutaneous cancers decreased with the combination therapy.

Interpretation
The addition of cobimetinib to vemurafenib was associated with a significant improvement in progression-free survival among patients with BRAF V600–mutated metastatic melanoma, at the cost of some increase in toxicity.

2.2 Nivolumab (BMS-936558, MDX1106, ONO4538) as first line therapy for unresectable or metastatic melanoma

Drug description: a fully human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1)

Incidence in Austria: advanced melanoma 640/year

EMA/FDA licensing for this indication: -/-

Phase III results:

Robert et al.*Nivolumab in Previously Untreated Melanoma without BRAF Mutation* NEJM (2014) - online first; DOI: 10.1056/NEJMoa1412082

Background
Nivolumab was associated with higher rates of objective response than chemotherapy in a phase 3 study involving patients with ipilimumab-refractory metastatic melanoma. The use of nivolumab in previously untreated patients with advanced melanoma has not been tested in a phase 3 controlled study.

Methods
We randomly assigned 418 previously untreated patients who had metastatic melanoma without a BRAF mutation to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab- matched placebo every 2 weeks). The primary end point was overall survival.

Findings
At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drugrelated adverse events of grade 3 or 4 occurred in 11.7% of the patients treated with nivolumab and 17.6% of those treated with dacarbazine.

Conclusions
Nivolumab was associated with significant improvements in overall survival and progression-free survival, as compared with dacarbazine, among previously untreated patients who had metastatic melanoma without a BRAF mutation.

3 Cervix cancer

Bevacizumab (Avastin®) for stage IVB, recurrent or persistent carcinoma of the cervix

Drug description: anti-VEGF antibody

Incidence in Austria: 390 patients

EMA/FDA licensing for this indication: -/-

Phase III results: Tewari et al. *Improved Survival with Bevacizumab in Advanced Cervical Cancer* N Engl J Med (2014) 370; 734-743;

Background

Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab, a humanized anti-VEGF monoclonal antibody, has single-agent activity in previously treated, recurrent disease. Most patients in whom recurrent cervical cancer develops have previously received cisplatin with radiation therapy, which reduces the effectiveness of cisplatin at the time of recurrence. We evaluated the effectiveness of bevacizumab and nonplatinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

Methods

Using a 2-by-2 factorial design, we randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg per kilogram of body weight. Chemotherapy consisted of cisplatin at a dose of 50 mg per square meter of body-surface area, plus paclitaxel at a dose of 135 or 175 mg per square meter or topotecan at a dose of 0.75 mg per square meter on days 1 to 3, plus paclitaxel at a dose of 175 mg per square meter on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a complete response was documented. The primary end point was overall survival; a reduction of 30% in the hazard ratio for death was considered clinically important

Results

Groups were well balanced with respect to age, histologic findings, performance status, previous use or nonuse of a radiosensitizing platinum agent, and disease status. Topotecan–paclitaxel was not superior to cisplatin–paclitaxel (hazard ratio for death, 1.20). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% confidence interval, 0.54 to 0.95; P=0.004 in a one-sided test) and higher response rates (48% vs. 36%, P=0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%).

Conclusion

The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival.